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Insight into the Copper-Catalyzed Borylation of Strained Alkenes.

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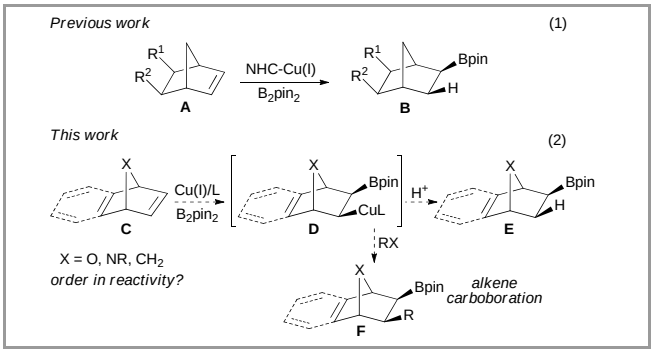
Abstract: The copper-catalyzed hydro- and carboboration of strain alkenes is presented. The reaction is highly diastereoselective and affords boronic ester derivatives many of which are difficult to synthesize by known methods. Competition experiments with different alkenes show that high levels of chemoselectivity can be achieved. DFT calculations are in agreement with the observed chemoselectivity.

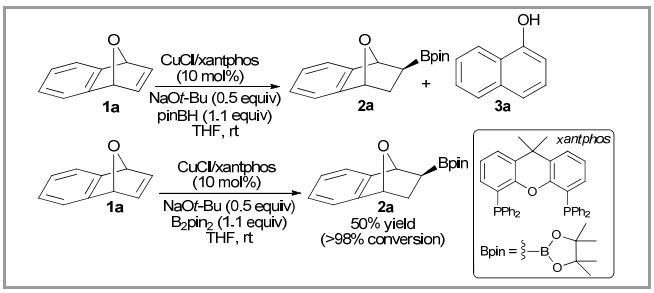
Key words: Bicyclic compounds, boron, catalysis, chemoselectivity, copper.

The development of efficient and stereoselective catalytic methods to form carbon-boron bonds is a compelling challenge in organic synthesis.[1] In the last decade, copper-catalyzed borylation reactions have emerged as a powerful new tool for the synthesis of boronic ester derivatives.[2] Despite the extensive efforts made in this field, there are some challenges yet to be addressed, especially those related with the hydroboration of non-activated olefins.[3] Theoretical studies indicate that the olefin acts predominantly as a π-Lewis acid in this class of transformations.[4] The LUMO (π* orbital) of the alkene must be low enough in energy to interact with the HOMO of the copper-boryl complex. In this context, Mcquade has recently shown that NHC-Cu complexes are able to promote the hydroboration of norbornene derivatives **A**.[5] In light of this result, we were intrigued by the idea of extending the copper-catalyzed hydroboration to alkenes with different degree of strain and to establish, if possible, an order in reactivity. In particular, we focused our attention on benzonorbornadienes derivatives **C**. These substrates were particularly interesting for two reasons: First, boronic esters **E** have not been previously synthesized by standard borylation procedures. Second, the oxa- (X = O) and aza- (X = NR) benzonorbornadiene derivatives present an additional challenge since copper-catalyzed additions of nucleophiles are known to give ring-opened products.[6,7] Herein, we demonstrate that a readily available phosphine-copper complex effectively catalyzes the hydroboration of benzonorbornadienes **C**. We have also extended our study to norbornenes and norbornadienes with different degrees of strain and have established an order in reactivity between them. Additionally, we have shown that the bicyclic alkyl copper intermediate **D** can react with MeI with excellent diastereoselectivity.



Scheme 1. Copper-catalyzed hydroboration of strained alkenes

We began by examining the reactivity of oxabenzonorbornadiene **1a** under copper-catalyzed borylation conditions using pinacol borane (pinBH).[3c,d] Unfortunately, using CuCl (10 mol%), xantphos (11 mol%), pinBH (1.1 equiv), and NaO*t*-Bu (0.5 equiv.) in THF, we obtained a mixture of the desired compound **2a** and the ring-opened product **3a**. We then searched for conditions using bispinacolatodiboron (B_2pin_2) as the boron source. Gratifyingly, in the presence of CuCl (10 mol%), xantphos (11 mol%), B_2pin_2 (1.1 equiv), NaO*t*-Bu (0.5 equiv.) and MeOH (4 equiv) in THF, we observed the formation of boronic ester **2a** with excellent diastereoselectivity and without observing ring-opened products. The conversion was high but the yield was only moderate due to partial decomposition of the product during the purification process.

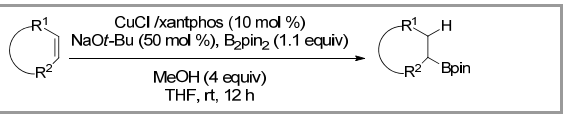


Scheme 2. Copper-catalyzed hydroboration of **1a**

With these conditions in hand, we decided to study the influence of the bridgehead atom as well as the strain of the alkene in the borylation reaction (Table 1). Aza- and carbobicyclic alkenes **1b** and **1c** showed similar behavior affording **2b** and **2c** as single compounds.

Less strained oxanorbornene **1d** also gave boronic ester **2d** in good yield. Norbornadiene **1e** selectively afforded the monoborylated product **2e** when using 1 equivalent of bis(pinacolato)diboron. Similarly, with two equivalents of B_2pin_2 the bisborylated product was obtained. This approach notably improves the reported synthesis of **2e**, previously prepared as an *endo*:*exo* mixture of diastereomers through a Diels-Alder cycloaddition.[8] Norbornene **1f** reacted smoothly under the conditions described above to give boronic ester **2f** in excellent yield. Additionally, from cyclopentadiene dimer **1g**, we observed exclusive borylation of the more strained alkene. Finally, when we moved to less strained alkenes, we observed a noticeable decrease in reactivity (Table 1, entries 3-5). Cyclopentene **1h** afforded boronic ester **2h** in only 16% yield while cyclohexene **1i** did not react under the conditions described above.

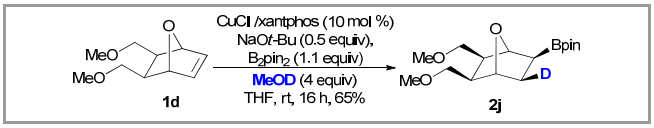
Table 1. Copper-catalyzed hydroboration of strained alkenes



Entry	Alkene	Product	Yield%[a]
1	**1a**	**2a**	50 (>98)[b]
2	**1b**	**2b**	54 (>98)[b]
3	**1c**	**2c**	50 (>98)[b]
4	**1d**	**2d**	65 (>98)[b]
5	**1e**	**2e**	75
6	**1f**	**2f**	75
7	**1g**	**2g**	84[c]
8	**1h**	**2h**	16[d]
9	**1i**	**2i**	<2[d]

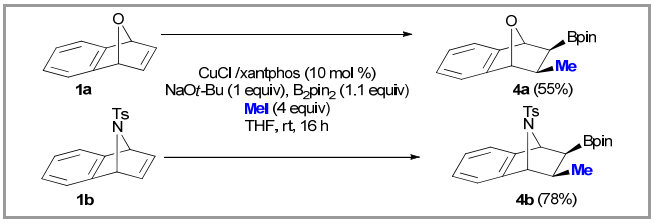
[a]Yield of isolated products; Unoptimized reaction times. [b]Conversion determined by analysis of ^{1}H NMR spectra of crude products. [c]Obtained as a 69:31 mixture of regioisomers. [d]Conversion determined by GC using an internal standard.

In the presence of MeOD, oxabicycle **1d** afforded compound **2j** in 65% yield as a single diastereomer (Scheme 3, >98% D incorporation). The diastereoselective formation of the C-D bond reveals the potential to capture the intermediate alkylcopper species **D** (Scheme 1) with electrophiles other than proton.



Scheme 3. Deuteration experiment with bicycle **1d**

This result led us to explore the possibility of using an an alkyl halide, such as MeI, instead of MeOH to form a C-B and a C-C bond in a single catalytic cycle (Scheme 5).[9] After several experimentation, we were please to find that the use of CuCl (10 mol%), xantphos (11 mol%), B_2pin_2 (1.1 equiv), NaO*t*-Bu (1.1 equiv) and MeI (4 equiv) in THF, afforded bicyclic alkenes **4a** and **4b** in good yields as single diastereomers (Scheme 5). As we and others previously observed for the carboboration of alkynes,[10] the use of one equivalent of NaO*t*-Bu was crucial in this transformation as it regenerates the copper alkoxide species involved in the catalytic cycle. The use of less than one equivalent of base resulted in lower conversions. In all cases, the diastereomer resulting from the *syn* addition of the methyl and boron groups was formed with complete selectivity. As above, we did not observe any traces of ring-opened products in the ^{1}H NMR of the crude mixtures.



Scheme 4. Copper-catalyzed carboboration of strained alkenes

Next, we decided to run competition experiments to see what level of chemoselectivity could be achieved in the copper-catalyzed borylation of strained alkenes. To do so, an equimolecular mixture of two strained alkenes was subjected to copper-catalyzed hydroboration conditions [CuCl (10 mol%), xantphos (11 mol%), NaO*t*-Bu (0.5 equiv) and MeOH (4 equiv)] with a deficiency of B_2pin_2 (0.5 equiv). After 12 h, the borylated products ratio was measure in the ^{1}H NMR crude. First, we selected alkenes **1a** and **1c** to study the effect of the bridgehead atom in the copper-catalyzed hydroboration. Surprisingly, we did not see any signals corresponding to **2c** in the ^{1}H NMR spectra of the crude product and boronic ester **2a** was the only product obtained (competition 1). This result reveals the profound influence of the oxygen atom in the reactivity of these bicycles. Starting from an equimolecular mixture of alkenes **1a** and **1d**, with the same bridgehead atom but different degree of strain, we observed exclusive formation of

2a (competition 2). Therefore, the ring strain is also playing an important role in the reactivity. Bicycles **1c** and **1e**, with the same bridgehead and similar degree of strain, afforded a 62:38 mixture of **2c** and **2e** (competition 3). The strong influence of the oxygen atom was further shown in competition 4. A mixture of alkenes **1d** and **1e** afforded oxygenated bicycle **2d** with high chemoselectivity. Finally, competition 5 confirms that norbornadiene **1e** is more reactive than non-strained styrene derivative **1k**. With these results and those obtained in Table 1 we have established the order in reactivity shown in Figure 1 with the oxa-derivatives **1a** and **1d** being the most reactive .[11] The complete chemoselectivity observed in most cases is striking and could be useful for site-selective functionalizations.

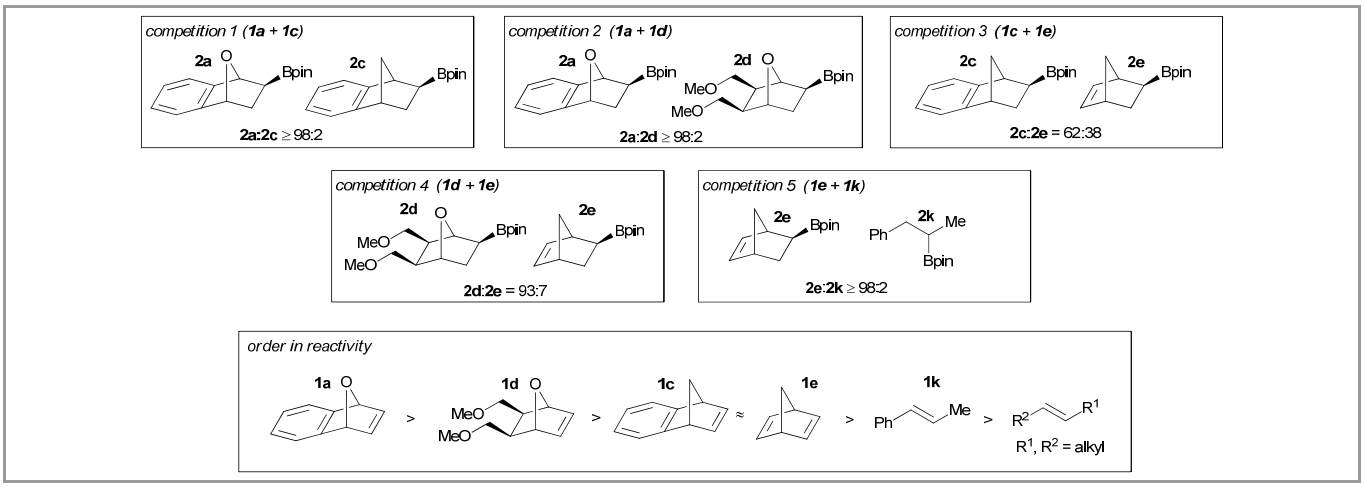


Figure 1. Competition experiments

To gain further insight into the role of the bridgehead atom, we analyzed by DFT calculations the frontier molecular orbitals for benzonorbornadienes **1a** and **1c** (Figure 2). As mentioned above, previous theoretical studies indicate that the olefin acts predominantly as a π-Lewis acid in the copper-catalyzed hydroboration of alkenes.[4] Therefore, the LUMO (π* orbital) of the alkene interacts with the HOMO (σ orbital) of the copper-boryl species. The lower lying LUMO of the oxabenzonorbornadiene **1a** derivative makes it a better electrophile than **1c** which is in agreement with the higher reactivity observed for **1a** (Figure 1, competition 1).

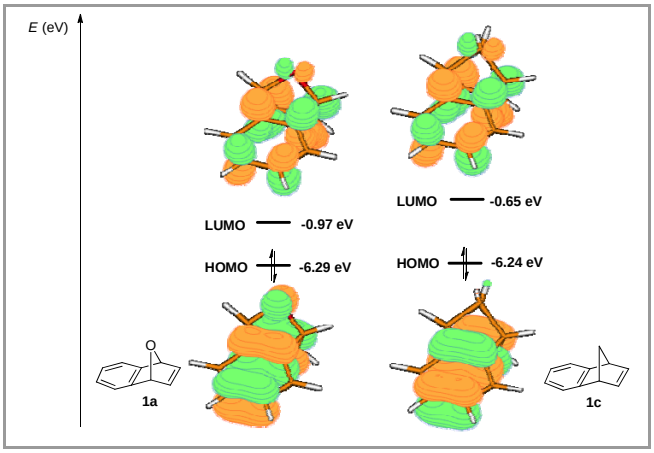


Figure 2. Frontier molecular orbitals and energies (in eV) for alkenes **1a** and **1c** computed at the B3LYP/6-311++G(d,p) level of theory including solvent effects over the geometry obtained at the B3LYP/6-31G(d) level.

Additionally, in order to investigate the energetics related to the insertion of the alkene into the Cu-B bond, we carried out DFT calculations using alkene **1a** and the model Cu-boryl complex **G** (Figure 3). We simplified the calculations by substituting the methyl groups in the phosphine ligand and in the Bpin ligand with hydrogen. We found a two-step mechanism with a first transition state **TSI-1a** corresponding to the

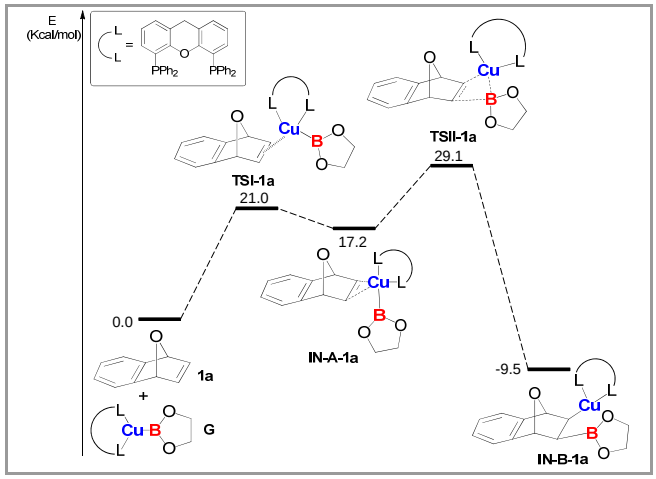


Figure 3. Energetic profile for the reaction of **1a** with Cu-boryl complex **G**. Gibbs free energies are referred to the reactants and are given in kcal/mol. They have been computed at the B3LYP/6-311++G(d,p) level of theory including solvent effects over the geometry obtained at the B3LYP/6-31G(d) level.

complexation of the Cu-boryl complex to the alkene and a second transition state **TSII-1a** corresponding to the insertion of the alkene into the Cu-B bond.[12]

Finally, we compared the energetic profile for the complexation and insertion in alkenes **1a**, **1c**, **1e** and **1l** (Figure 4). In all cases, the complexation transition state **TSI** showed lower energy than the insertion transition state **TSII**. In the oxa derivatives **1a** and **1l**, the transition states for insertion **TSII** and the intermediates **IN-B** are at lower energies than in the corresponding non-oxa- cases **1c** and **1e**. This is consistent with the LUMO energies and with the competition experiments. In summary, we have demonstrated that bicyclic alkenes with different degrees of strain can undergo copper-catalyzed hydroborations. Some of the examples described above represent boronic esters that have not been previously prepared using standard hydroboration conditions. We have also demonstrated that alkylcopper intermediate species, formed in this transformation, can react with electrophiles other than a proton. Interestingly, we have carried out experiments to establish the order of reactivity of different strained olefins. These experiments are also supported by computational studies. We believe this study could be useful in other metal-catalyzed reactions involving the π* orbital of the alkene. The development of enantioselective versions of the transformations described above is underway.

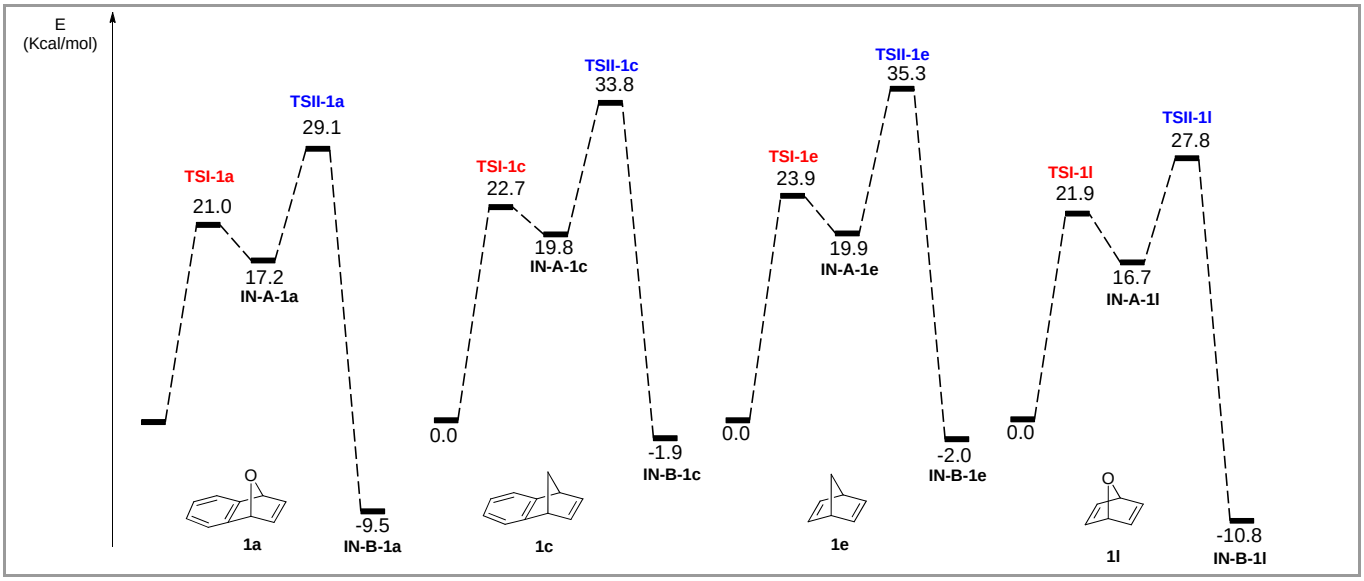


Figure 4. Energetic profile for the reaction of **1a**, **1c**, **1e** and **1l** with Cu-boryl complex **G**. Gibbs free energies are referred to the reactants and are given in kcal/mol. They have been computed at the B3LYP/6-311++G(d,p) level of theory including solvent effects over the geometry obtained at the B3LYP/6-31G(d) level.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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